Chronic valproic acid intoxication: reversal by naloxone

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A 76-year-old woman being treated with sodium valproate for bipolar depression presented with a 4 day history of acute confusion and tremulousness. She had apnoeic episodes, reduced conscious level and generalised myoclonic movements. Her plasma valproate concentration was 848 μmol/l (normal 300–600 μmol/l). Administration of naloxone 0.8 mg led to rapid clinical improvement. Naloxone may be useful in reversing the features of chronic valproate toxicity.

A 76-year-old woman presented to our emergency department with a 4 day history of general malaise, confusion and increasing tremor. She had a history of type 2 diabetes mellitus, ischaemic heart disease and pacemaker insertion for complete heart block. She also suffered from bipolar depression which was treated with sodium valproate. The dose had been increased from 500 mg to 750 mg twice daily 3 months previously. As a result of her confusional state, she had taken her total daily dose that morning. Her medication (aspirin, simvastatin, furosemide, olanzapine, ramipril and sodium valproate) was dispensed weekly and she was on a supervision order.

On examination, she was apyrexial and looked clinically dehydrated. Her heart rate was 70/min, blood pressure 70/40 mm Hg and respiratory rate 16–20/min. Brief apnoeic episodes and generalised myoclonic movements were noted. At presentation, she was drowsy with a Glasgow Coma Score (GCS) of 14/15, but her conscious level worsened subsequently (her GCS dropped to 10/15). Her haemoglobin, white cell count, electrolytes and liver function tests were normal. She had an elevated urea of 10.4 mmol/l, reduced platelet count of 61×10^9/l and valproate concentration 848 μmol/l (normal 300–600 μmol/l). *Escherichia coli* was cultured from a urine specimen sent by her general practitioner.

A diagnosis of urinary tract infection and concomitant valproate intoxication was made. The patient was treated initially with ciprofloxacin. The units for the valproate concentration were not sought by the admitting medical team and the reported concentration was thought to represent a severe acute intoxication. She was transferred to the intensive care unit with a view to invasive monitoring and institution of haemodialysis in the event of subsequent deterioration. In the interim, TOXBASE (http://www.toxbase.org), the NPIS on-line poisons information database, was consulted and the use of naloxone for apnoeic spells was noted by the medical team. Administration of an intravenous bolus of 0.8 mg naloxone led to a rapid improvement in conscious level (GCS 14/15), resolution of her apnoeic episodes and improvement in blood pressure to 110/70 mm Hg. A naloxone infusion was administered and the patient recovered over the next 24 h, without any sequelae.

DISCUSSION

This is the first reported case of chronic valproic acid toxicity reversed by administration of naloxone. It also highlights the dangers associated with inconsistent use of units of measurement in hospital laboratories. This patient was thought to have life-threatening acute valproic acid intoxication as plasma concentrations of >850 mg/l have been reported to cause serious complications such as coma.[1] This arose as a result of misinterpretation of the plasma concentration in SI units (mg/l) although, in the measured units (μmol/l), this only represented moderate chronic intoxication.

Although it is not possible to exclude the possibility of opiate toxicity in this case, this patient did not have a history of opiate abuse and it is unlikely that she would have had access to other prescription-only medication as she was receiving close supervision because of her mental illness.

The use of naloxone in reversing features of valproic acid toxicity following acute intoxication has been reported in several cases. In most cases, the toxicity was mild with plasma valproic acid concentrations ranging from 138–185 mg/l, with one case of successful use in a 21-year-old with a peak plasma concentration of 487.8 mg/l where rapid improvement in conscious level was seen after naloxone on two occasions 30 min apart (table 1). On the other hand, in cases of severe valproate intoxication with plasma concentrations exceeding 850 mg/l, administration of naloxone has been unsuccessful, and haemodialysis may be required to enhance elimination.[2]

Valproic acid is thought to enhance the action of γ-aminobutyric acid (GABA) in the brain leading to its anticonvulsant effect. It is also possible that valproic acid may act on opioid receptors and increase release of endogenous opioids. This may account for its analgesic and mood stabilising effects. It has been postulated that naloxone, in addition to opioid receptor antagonism, may either act as a GABA antagonist[3] or may inhibit postsynaptic GABA transport due to valproic acid.[4]

Table 1 Case reports of naloxone use in acute valproic acid toxicity

Reference	Age of patient	Plasma valproate concentration (mg/l)	Naloxone dose	Response to naloxone
Steiman *et al* 1979	19 months	185	0.01 mg/kg	Coma reversed after 3 min. After 20 min, somnolence reversed with a second dose
Espinoza *et al* 2001	3 years	Not recorded	0.1 mg	Coma and respiratory depression reversed within minutes
Roberge *et al* 2001	44 years	138	2 mg	Obtundation reversed; response to a second dose after relapse at 1 h
Alberto *et al* 1989	22 years	180.4	2 mg	Somnolence and respiratory depression reversed in 1 min
Montero 1999	21 years	487.8	0.4 mg then 0.8 mg	Improvement in conscious level within minutes on both occasions

Key practice points

- Naloxone may be used to reverse features of mild to moderate valproic acid toxicity.
- Particular attention should be paid to units of measurement when interpreting plasma drug concentrations.

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IMAGES IN EMERGENCY MEDICINE

Cutaneous larva migrans in England: a case in a returning traveller

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A 17-year-old man presented with a history of insect bite to his right foot 1 week ago. He had recently returned to the UK from Kenya after a holiday. A serpiginous elevated tunnel-like erythematous skin lesion was seen on the sole of his foot (fig 1). The patient thought it was an insect and tried to lance it out himself (leaving two puncture holes as shown in the fig) but was unsuccessful. The clinical diagnosis was cutaneous larva migrans.[1]

Cutaneous larva migrans—also known as ground itch or sandworm disease—is a dermatosis caused by accidental percutaneous penetration and subsequent migration of larvae of various nematode parasites.[2] The disease is restricted to the epidermis and is self-limiting; rarely pulmonary eosinophilia and secondary bacterial infection can occur. Treatment is cryotherapy or anti-parasitic medication with thiabendazole. The eruption generally disappears after 1–2 months, but may present for 6 months or longer.

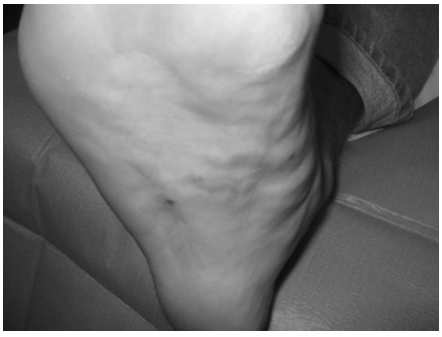

Figure 1 Lesion on sole of foot caused by cutaneous larva migrans. Informed consent was obtained for publication of this figure.

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